Modern management in fetal ventriculomegaly diagnosed in the second trimester of pregnancy

Abstract

Ventriculomegaly (VM) is the most common central nervous system abnormality identified on prenatal sonography. It is clinically important because it can be caused by a variety of disorders that result in neurological, motor, and/or cognitive impairment. Many cases are associated with other abnormal findings, but in some fetuses, VM is the only abnormality. If abnormalities are found, parents need as much accurate information as possible to assist in making decisions about the future of pregnancy. In the present review, we present an up-to-date clinical opinion regarding the management of fetal VM.

Keywords: *ventriculomegaly, management, ultrasound, MR*

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Introduction

Central nervous system (CNS) malformations are one of the most common of all congenital anomalies. The incidence of neural tube defects is estimated to be 1-2 at 1000 births, but the real one can be about 1 at 100 because of a large variaty of intracranial abnormalities with intact neural tube which are likely to escape detection at birth and to become manifest in later life.

The etiology of these abnormalities is multifactorial as they can be due to a single mutant gene (Meckel Syndrome, median cleft-face syndrome, syndrome of anterior sacral meningomyelocele), chromosomial abnormalities (trisomy 21, 13, 18), teratogenic agents (valproic acid, thalidomide, carbamazepine), maternal diabetes mellitus or materno-fetal infections (toxoplasmosis, cytomegalovirus, varicella zoster virus, parvovirus B19, rubella)[1].

Structural abnormalities of fetal brain are investigated in many countries by using ultrasonography, first by way of screening programs and then by detailed anomaly scanning on certain centers. Imaging of the fetal brain is routinely performed by using sonography. Finding no abnormality can be of great confort for parents, particulary if the fetus is at increased risk of malformation. If abnormalities are found, parents need as much accurate information as possible to assist in making decisions about the future of pregnancy. This is why magnetic resonance imaging (MR) of the fetal brain has been shown to provide additional diagnostic information and it is a modern and useful instrument for accurate diagnostic of fetal intracranian defects[2].

Ventriculomegaly, a commom central nervous system abnormality

Ventriculomegaly (VM) is the most common CNS abnormality identified on prenatal sonography[3]. The causes of ventriculomegaly are very heterogenous and include developmental, destructive and obstructive processes. As many as 80% of fetuses with ventriculomegaly have additional abnormalities that are detected by prenatal sonography and/or postnatal evaluation[4]. Additional abnormalities include chromosomal, extra-CNS and CNS anomalies. The neurodevelopmental outcome of fetal ventriculomegaly depends, at least in part, on the presence of additional abnormalities identified either in utero or at birth. In a large study of sonographically isolated ventriculomegaly, Gupta et al. reported thet the incidence of developmental delay was 37% in children with isolated VM, compared with 84% in children whom additional abnormalities were identified at birth. Neurodevelopmental disabilities can occur in 0-36% of children with isolated VM and some studies have found that the risk of developmental delay is lower if the atrial diameter is less than 12 mm and if the fetus is male[5] (Figures 1, 2, 3, 4 and Table 1).

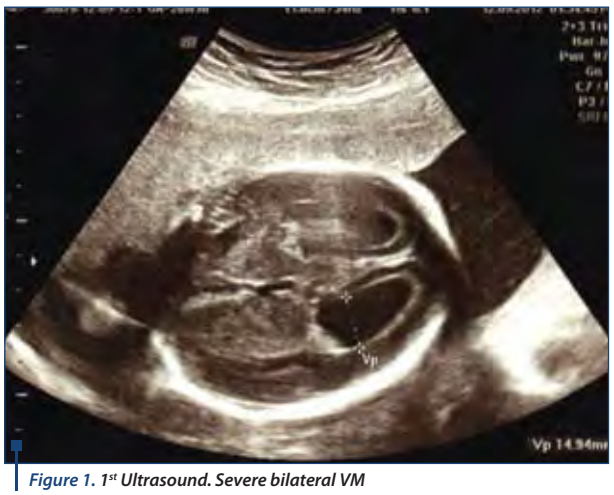

Figure 1. 1st Ultrasound. Severe bilateral VM

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The wide definition of fetal VM is a transtrigone measurement of ≥10 mm at any stage of pregnancy; this is the defined as atrial width larger than 10 mm on sonogram, measured at the posterior margin of the glomus of the choroid plexus on an axial plane through the thalami[6]. Values from 10-12 mm indicates mild VM, 12-15 mm indicates moderate VM and over 15 mm means severe VM.

The importance of precise and accurate measurements of the trigone relates to the known risk of poor postnatal outcome. It is widely accepted that severe VM is over 15 mm but there is disagreement about the classification of VM of 10-15 mm. Many researchers and clinical practitioners use mild VM to describe any trigone measurement of 10-15 mm inclusive because this approach is supported with metaanalisys finding that the fetuses showing isolated VM of ≤12 mm do not have a statistically significant better neurologic prognosis compared with those of 12-15 mm[7]. Melchiorre et al. describe a 16.6% risk of poor outcome in the 10-12 mm group and 11.8% in the 13-15 mm group. There are recent reports that showed a different risk of associated abnormalities of 6% in supposed isolated mild VM and 14% in moderate VM and this is why we use better this classification[8]. Althought the atrial diameter is relatively constant between 15 and 35 weeks of gestation, the relative size of the lateral ventricles decreases with increasing gestational age causing the ventricles to appear larger early in gestation. Fetal MR measurement of atrial diameter is usually within 2 mm of sonographic measurements even when MR examination and sonogram are performed in the same moment. With this definition, VM is found in ≤2,5/1000 pregnancies[1]. In some cases, VM is the only abnormal findings (isolated VM) which is found in about 20% of all cases of all fetal VM diagnosed on sonography. But, according with certain studies, in about 17% of sonografical isolated VM, MR discovered associated abnormalities during pregnancy[1]. Fetal with isolated VM are at an increased risk of aneuploidy, particulary trisomy 21, and amniocentesis is offered for this reason[9]. It is of great importance to recognise VM antenatally because it may be an indicator and/or manifestation of other CNS abnormalities with values of 88% sensitivity. Fetal VM is associated with poor outcome in terms of mortality and morbidity if projected outcome data from termination of pregnancy cases are included. When the VM is the only abnormality and the fetus is known to be euploid, counseling parents is partly based on the severity of the VM because increasing size of the ventricles is associated with higher risk of poor outcome. The most recent data on outcome have used the results of in utero MR imaging to define isolated VM and modern management of these cases is to include in utero MR in the diagnostic pathway for fetuses with VM on antenatal ultrasound with a significant effect on clinical management[10]. Sonographically ocult findings include developmental abnormalities such as agenesis of the corpus callosum, cortical malformations, periventricular nodular heterotopia, cerebellar dysplasia, partial agenesis of the septum pellucidum and destructive abnormalities sunch as periventricular leukomalacia, porencephaly,

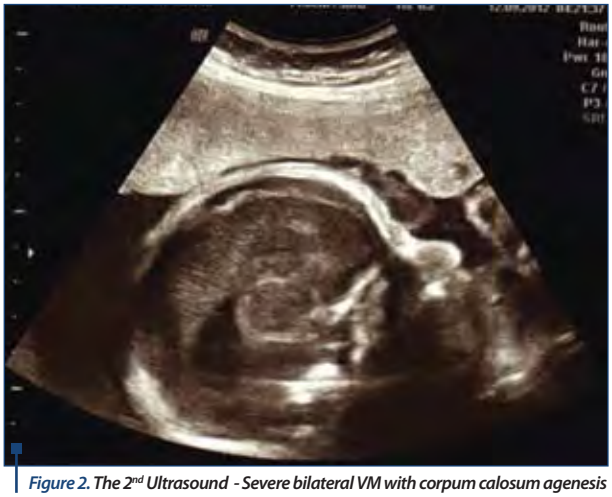

Figure 2. The 2nd Ultrasound - Severe bilateral VM with corpum calosum agenesis

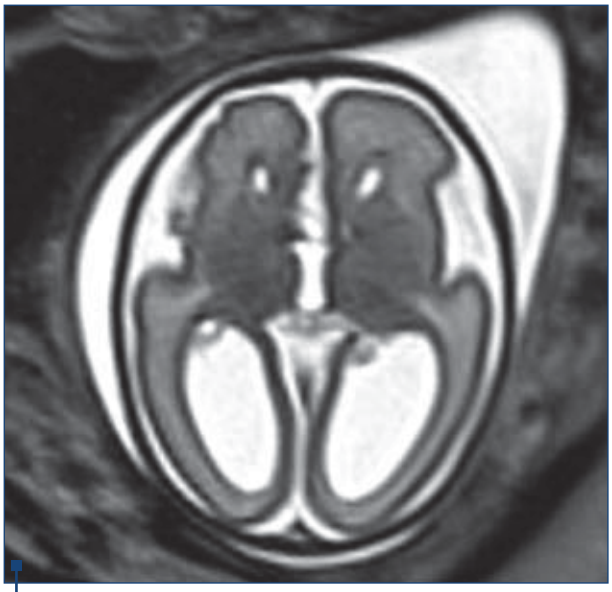

Figure 3. The 1st MR - Severe bilateral VM with corpum calosum agenesis

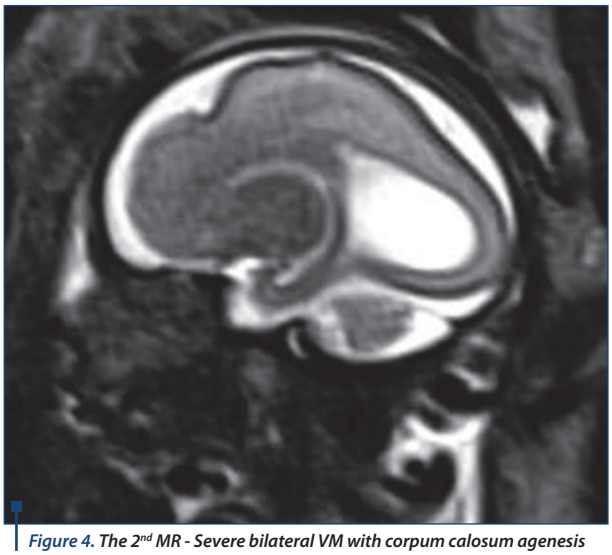

Figure 4. The 2nd MR - Severe bilateral VM with corpum calosum agenesis

multicystic encephalomalacia, intraventricular hemorrage and subependymal hemorrhage.

There are a lot of studies tring to establish the diagostic management of the cases with VM diagnosed at the ultrasound exam at about 20 weeks of gestation and what is the best way for counseling the parents.

Some of these studies include pregnant women recruited from the tertiary assesment units with aparently isolated VM at 20-24 weeks. They all have done fetal intrauterine MR which discovered other brain abnormalities in about 17-32% from all the cases[1,11,12]. Only in 2-4% from the cases there were disagrements between the diagnosis of VM, in terms of mild, moderate or severe VM. The most freguently associated abnormalities was agenesis of the corpum calosum and isolated microcalcifications around the ventricles.

All these studies have accepted that severe categories of VM was associated with higher risk of poor outcome; fetuses with isolated VM confirmed by intrauterin MR have 95.4-97.7% chance for beeing alive at 2 years if VM is mild, 80.2%-83.2% if VM is moderate and 32.1-33.3% if VM is severe. Of those that were alive, neurodevelopmental outcome was normal in 93% of mild cases, 75% of moderate and 62.5% of severe VM cases[1,11,12]. Ouahba J et al. found in a study on 167 cases of isolated ventriculomegaly that intrauterine MR is able to diagnose all the cases of associated CNS abnormalities with a certain higer rate than ultrasound exam[13].

Another study of Gupta et al. described 276 cases of apparent isolated VM all of whom were delivered. They found a 70% survival rate and about 59% were developmentally normal. A recent study of Falip et al. who incorporated untrauterin MR in evaluation of all his cases (and he make a very accurate prenatal diagnostic of isolated VM) showed that the outcome of an isolated VM was excellent in fetuses with 10-11.9 mm trigones in 94% of cases and in 85% of cases with trigone measurements of 12-15 mm[14].

Some studies were performed to find what is the management in second trimester diagnosed VM for a corect counseling and what kind of investigations shoud be done to complete the therpeutic approach. Griffith et al. had repeated the intrauterine MR for 46 women diagnosed with VM between 20-24 weeks. All these pacients had first intrauterine MR at the first ultrasound exam. In 5 cases they diagnosed at the first MR associated anbnormalities as following: agenesis/hypogenesis of *corpum calosum*, absent cavum pellucidum (one case) and cerebelar hipoplasia (one case). None of those diagnoses were changed on the basis of the second intrauterine MR (30-32 weeks). In the other cases (41) diagnosed in the second trimester to have isolated VM, only in one case the 30-32 weeks intrauterine MR had found an associated abnormality (hypogenesis of corpum calosum). The overall conclusion is that brain abnormalities other than VM would be obtained on a third trimester intrauterine MR imaging examination in only 10% of cases, and usually lower. The most severe abnormalities which are incompatible with live and normally mean that the issue of termination would be disscused, are 95-99% detectable at first ultrasound exam combined with intrauterine MR at 20-24 weeks[15]. By contrast, there are some investigators (Melchiorre et al.) that found an additional 12.8% extra pickup rate for the follow-up intrauterine MR in the third trimester[7].

Clinical findings regarding ventriculomegaly

The reviewers of the clinical significance of this findings commented that a woman would almost certainly have been offered fetal karyotiping on the basis of the imaging at 20-24 weeks, but all these studies revealed that is likely to have normal results[16] (Table 2).

In those cases with progessive fetal VM during pregnancy, ultrasound follow-up was very useful. Normalization is commonly seen in the 10-12 mm group (38-47%), compared with the 13-15 mm group (10-12%)[17]. In the group of 10-15 mm, stabilization appears in about

Table 1 Major cerebral anomalies diagnosed with MRA*

Anomalies diagnosed with MRI	N (5)	Cases also diagnosed by ultrasound examination
Third ventricle enlargement	6 (4.8)	2/6
Heterotopia	4 (3.2)	0/4
Septum pellucidum destruction	2 (1.6)	0/2
Partial agenesis of the *corpum calosum*	2 (1.6)	2/2
Agenesis of cerebelar vermis	1 (0.8)	0/1
Total	15 (12.2)	4/15

**Quahba J, Luton D, Vuillard E, Garel C, Gressens P, Blanc N, Elmaleh M, Evrard P, Oury J. Prenatal isolated mild ventriculomegaly: outcome in 167 cases . BJOG 2006; 113:1072-1079.*

75% of cases and progression in about 11% from all the cases. The pooled analysis performed by Melchiore et al. showed a progression rate of 16% of isolated VM, independent of size, and the developmental outcome was worse (44% rate of adverse outcome) that in the nonprogressive cases (7%)[7].

There are fewer published data concerning the rate of significance of assimetry of the fetal ventricles. The most studies showed a relatively high rate of unilateral VM.

Unilateral fetal VM was thought to be quite unusual in the older sonography literature, but it must be remembered that in many cases only the trigone furthest from sonography probe is measured or measured with certainty, because of the problems of "nearfield effect"[7]. This was reflected in a recent sonography and intrauterine MR imaging study in which unilateral VM was shown in 51/85 (60%) of fetuses with mild VM[18]. This was debated in the literature about the significance of unilateral isolated VM in fetus in relation with bilateral VM. Melchioree et al. analysed 5 published studies and came to the conclusion that there were no statistically significant differences of the outcome in terms of neurodvelopmental delay (6% in unilateral compared with 7.4% in bilateral)[7].

Asymmetric VM was largely defined in most studies as both trigones being ≥10mm but with a difference of ≥3mm between the 2 sides. Melchoirre et al. found the incidence of these cases of about 8% at 20-24 weeks and 15% at 30-32 weeks. Using the definition of mild VM as 10-15 mm, they found that fetuses with bilateral symmetric VM had 4% risk of developlmental delay while fetuses with bilateral asymmetric VM had poor outcome in 50% of cases[7,18]. It seems that furher studies including intrauterine MR will be usefull for counseling these couples[19-23].

Conclusions and future research

In our opinion, a correct diagnostic of fetal VM can be made using ultrasonography at 20-24 weeks.

Table 2 Paedriatic follow-up protocol

Paedriatic follow-up protocol
■ Examination at birt hand transcranial ultrasound at 3 days
■ Medical consultations at 2 months
■ Brain MR at 2 months
■ Medical consultations at 6, 9 months
■ Medical consultation at 1 year
■ Psychometric evaluation at 18 months
■ Brain MR before 2 years
■ Medical consultation at 2 years
■ Psychometric evaluation at 2 years
■ Medical consultation and psychometric evaluation each year

In all the cases with severe VM or progressive VM intrauterine MR should be done and the option of fetal kariotiping should be offered. The counseling of the parents depends by the moment of associated CNS abnormality or fetal abnormal kariotype and the possibility of termination of the pregnancy. Women with severe fetal VM (even isolated) should be advised about the high risks and poor outcome and perhaps offered termination of pregnancy irrespective of the information about brain malformation provided by MR. In isolated mild or moderate VM with nonprogressive measurement and without associated abnormalities the parents should be informed about the risk of developmental delays in 4-45% of cases, depending of the measurements and bilaterality. There is not any shown advantage in repeating intrauterine MR at 30-32 weeks of gestation in cases of isolated VM over and above the initial intrauterine MR findings at 20-24 weeks; the MR exam should be performed as soon as possible after the 20-24 weeks sonography. A modern and useful paedriatic follow-up protocol is shown in Table 2. ■

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